CARDIOLOGY

LECTURE – 2 : ACUTE CORONARY SYNDROME

Question Bank (Passmedicine , Pastest , Onexam) & Pastpaper informations are marked as RED

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CHEST PAIN: ASSESSMENT OF PATIENTS WITH SUSPECTED CARDIAC CHEST PAIN

NICE updated it's guidelines in 2016 on the 'Assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin'.

Below is a brief summary of the key points. Please see the link for more details.

Patients Presenting with Acute Chest Pain:

☑ **Immediate management of suspected acute coronary syndrome (ACS)**

- ✓ Glyceryl trinitrate
- ✓ **Aspirin 300mg.** NICE do not recommend giving other antiplatelet agents (i.e. Clopidogrel) outside of hospital
- ✓ Do not routinely give oxygen, only give if sats < 94%*
- ✓ Perform an ECG as soon as possible but do not delay transfer to hospital. A normal ECG does not exclude ACS

☑ **Referral**

- ✓ Current chest pain or chest pain in the last 12 hours with an abnormal ECG: emergency admission
- ✓ Chest pain 12-72 hours ago: refer to hospital the same-day for assessment
- ✓ Chest pain > 72 hours ago: perform full assessment with ECG and troponin measurement before deciding upon further action

☑ ***NICE suggest the following in terms of oxygen therapy:**

- ✓ Do not routinely administer oxygen, but monitor oxygen saturation using pulse oximetry as soon as possible, ideally before hospital admission. Only offer supplemental oxygen to:
- ✓ People with oxygen saturation (SpO2) of less than 94% who are not at risk of hypercapnic respiratory failure, aiming for SpO2 of 94-98%
- ✓ People with chronic obstructive pulmonary disease who are at risk of hypercapnic respiratory failure, to achieve a target SpO2 of 88-92% until blood gas analysis is available.

Patients Presenting with Stable Chest Pain:

☑ **NICE define anginal pain as the following:**

- ✓ 1. Constricting discomfort in the front of the chest, or in the neck, shoulders, jaw or arms
- ✓ 2. Precipitated by physical exertion
- ✓ 3. Relieved by rest or GTN in about 5 minutes

  - Patients with all 3 features have typical angina
  - Patients with 2 of the above features have atypical angina
  - Patients with 1 or none of the above features have non-anginal chest pain

For patients in whom stable angina cannot be excluded by clinical assessment alone NICE recommend the following (e.g. symptoms consistent with typical/atypical angina OR ECG changes):

- ✓ **1st line: CT Coronary Angiography**
- ✓ **2nd line: Non-invasive Functional Imaging (looking for reversible myocardial ischaemia)**
- ✓ **3rd line: Invasive Coronary Angiography**

☑ **Examples of Non-Invasive Functional Imaging:**

- ✓ Myocardial perfusion scintigraphy with single photon emission computed tomography (MPS with SPECT) or
- ✓ **Stress Echocardiography** or
- ✓ **First-pass contrast-enhanced Magnetic Resonance (MR) Perfusion** or
- ✓ MR imaging for stress-induced wall motion abnormalities

ACUTE CORONARY SYNDROME: A VERY BASIC INTRODUCTION

Acute coronary syndrome (ACS) is an umbrella term covering a number of acute presentations of ischaemic heart disease.

☑ It covers a number of presentations, including
- ✓ **ST elevation myocardial infarction (STEMI)**
- ✓ **Non-ST elevation myocardial infarction (NSTEMI)**
- ✓ **Unstable angina**
  - considered to be present in patients with ischaemic symptoms suggestive of an ACS and no elevation in troponins, with or without electrocardiogram changes indicative of ischaemia
  - however, as a rise in troponins may take some hours it may be indistinguishable for NSTEMI initially and is therefore treated the same until the troponin result is known

☑ Before we go into more detail into these presentations it's useful to take a step back and consider how such conditions develop.

ACS generally develops in patients who have ischaemic heart disease, either known or previously undetected. Ischaemic heart disease is a term synonymous with coronary heart disease and coronary artery disease. It describes the gradually build up of fatty plaques within the walls of the coronary arteries. This leads to two main problems:

- ✓ 1. Gradual narrowing, resulting in less blood and therefore oxygen reaching the myocardium at times of increased demand. This results in angina, i.e. chest pain due to insufficient oxygen reaching the myocardium during exertion
- ✓ 2. The risk of sudden plaque rupture. The fatty plaques which have built up in the endothelium may rupture leading to sudden occlusion of the artery. This can result in no blood/oxygen reaching the area of myocardium.

☑ Remember that there are a large number of factors which can increase the chance of a patient developing ischaemic heart disease:

Unmodifiable risk factors	Modifiable risk factors
Increasing age Male gender Family history	Smoking Diabetes mellitus Hypertension Hypercholesterolaemia Obesity

☑ Pathophysiology:

Ischaemic heart disease is a complex process which develops over a number of years. A number of changes can be seen:

- ✓ Initial endothelial dysfunction is triggered by a number of factors such as smoking, hypertension and hyperglycaemia
- ✓ This results in a number of changes to the endothelium including pro-inflammatory, pro-oxidant, proliferative and reduced nitric oxide bioavailability
- ✓ Fatty infiltration of the subendothelial space by low-density lipoprotein (LDL) particles
- ✓ Monocytes migrate from the blood and differentiate into macrophages. **These macrophages then phagocytose oxidized LDL, slowly turning into large 'foam cells'**. As these macrophages die the result can further propagate the inflammatory process.
- ✓ Smooth muscle proliferation and migration from the tunica media into the intima results in formation of a fibrous capsule covering the fatty plaque.

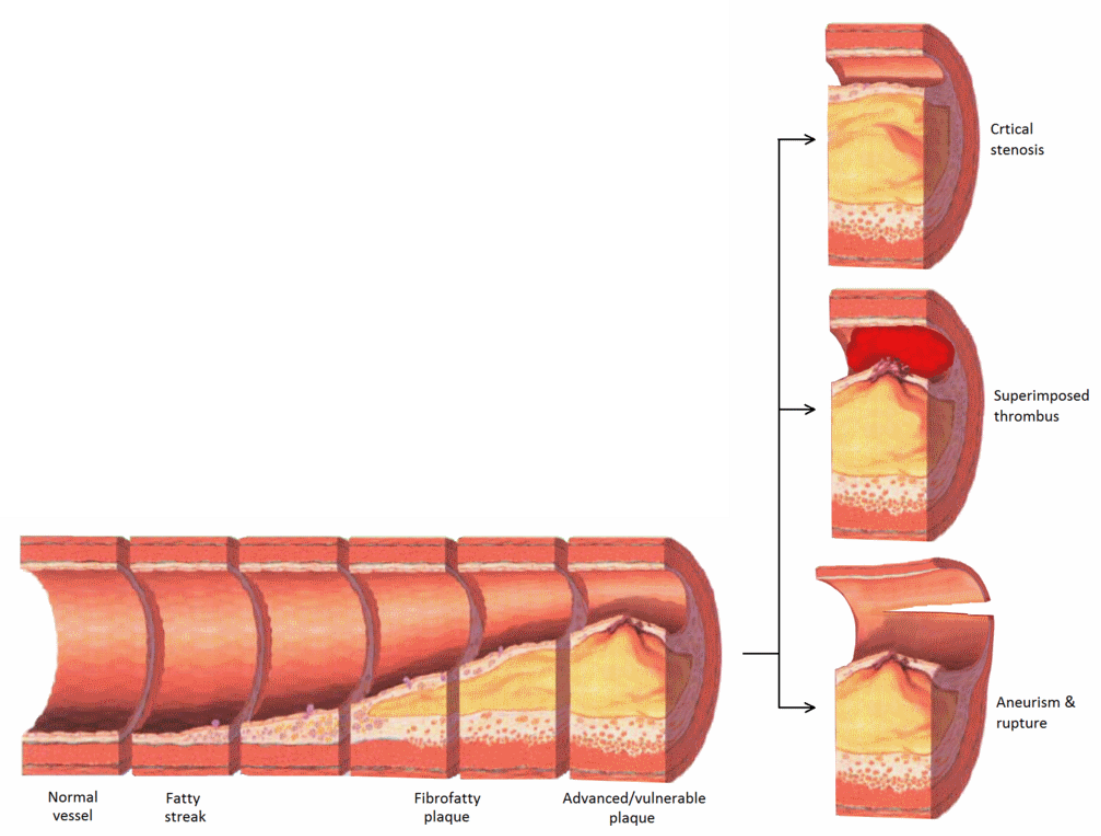
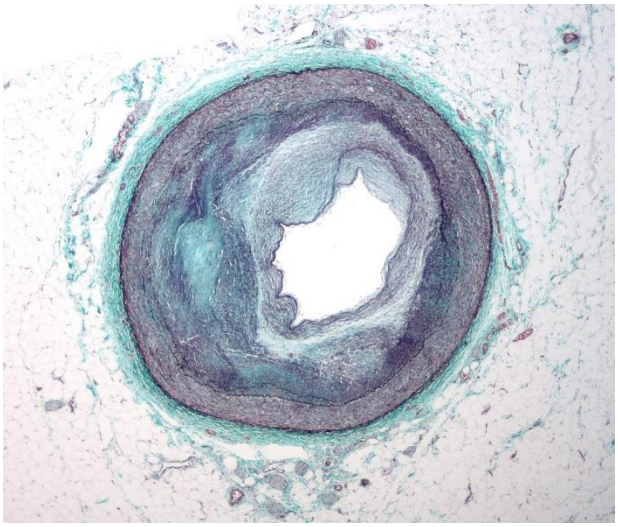


Diagram showing the progression of atherosclerosis in the coronary arteries with associated complications on the right.

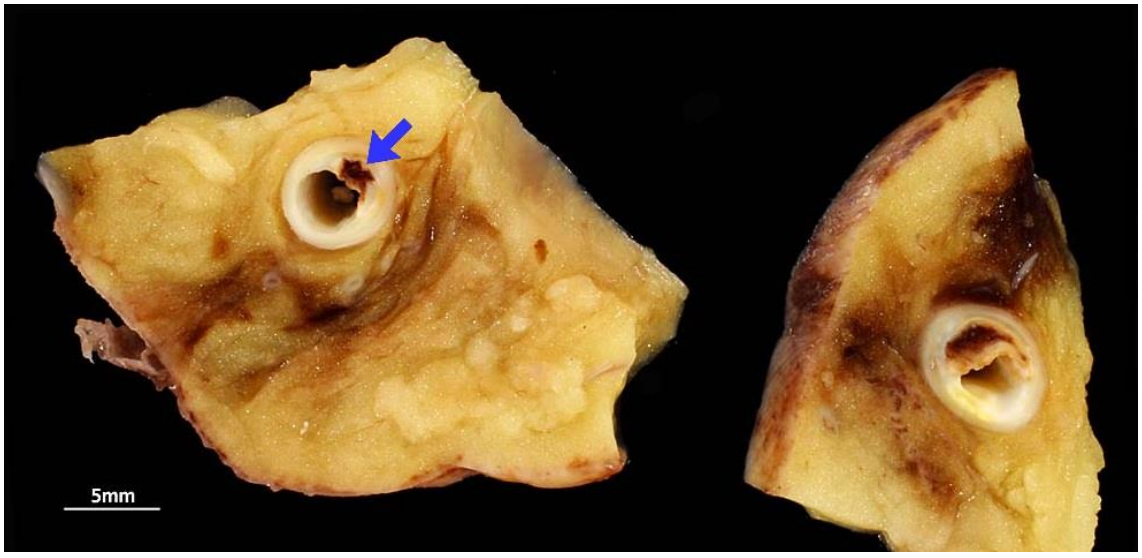


Slide showing a markedly narrowed coronary artery secondary to atherosclerosis. Stained with Masson's trichrome.

☑ Complications of atherosclerosis:

Once a plaque has formed a number of complications can develop:

- ✓ The plaque forms a physical blockage in the lumen of the coronary artery. This may cause reduced blood flow and hence oxygen to the myocardium, particularly at times of increased demand, resulting clinically in angina
- ✓ The plaque may rupture, potentially causing a complete occlusion of the coronary artery. This may result in a myocardial infarction



Ruptured coronary artery plaque resulting in thrombosis and associated myocardial infarction.

Pathological specimen showing infarction of the anteroseptal and lateral wall of the left ventricle. There is a background of biventricular myocardial hypertrophy.

☑ Symptoms and signs:

The classic and most common feature of ACS is chest pain.

- ✓ Typically central/left-sided
- ✓ May radiate to the jaw or the left arm
- ✓ Often described as 'heavy' or constricting, 'like an elephant on my chest'
- ✓ It should be noted however in real clinical practice patients present with a wide variety of types of chest pain and patients/doctors may confuse ischaemic pain for other causes such as dyspepsia
- ✓ Certain patients e.g. diabetics/elderly may not experience any chest pain

☑ Other symptoms in ACS include

- ✓ Dyspnoea
- ✓ Sweating
- ✓ Nausea and vomiting

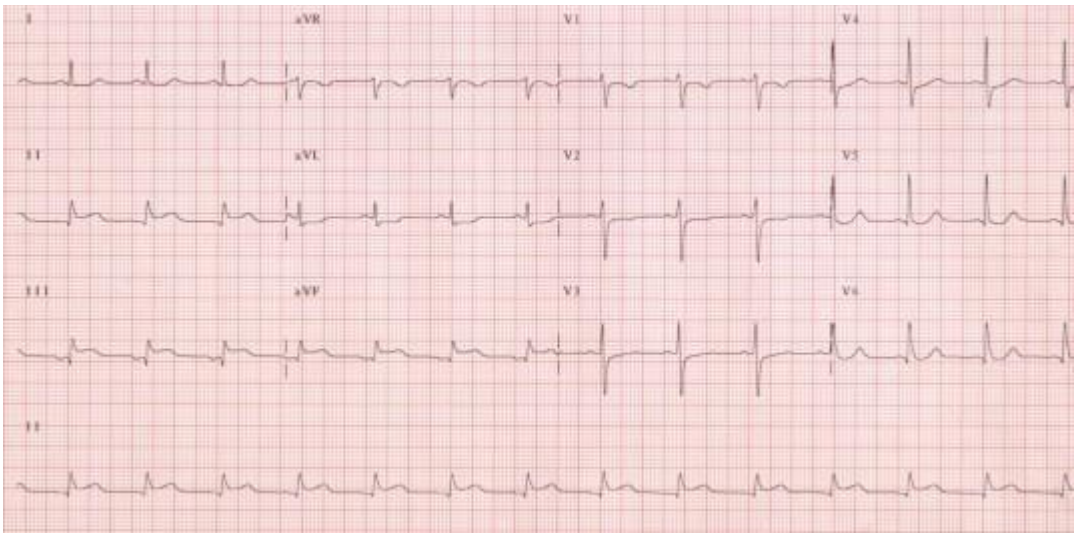
☑ Patients presenting with ACS often have very few physical signs to ellicit:

- ✓ Pulse, blood pressure, temperature and oxygen saturations are often normal or only mildly altered e.g. tachycardia
- ✓ If complications of the ACS have developed e.g. cardiac failure then clearly there may a number of findings
- ✓ The patient may appear pale and clammy

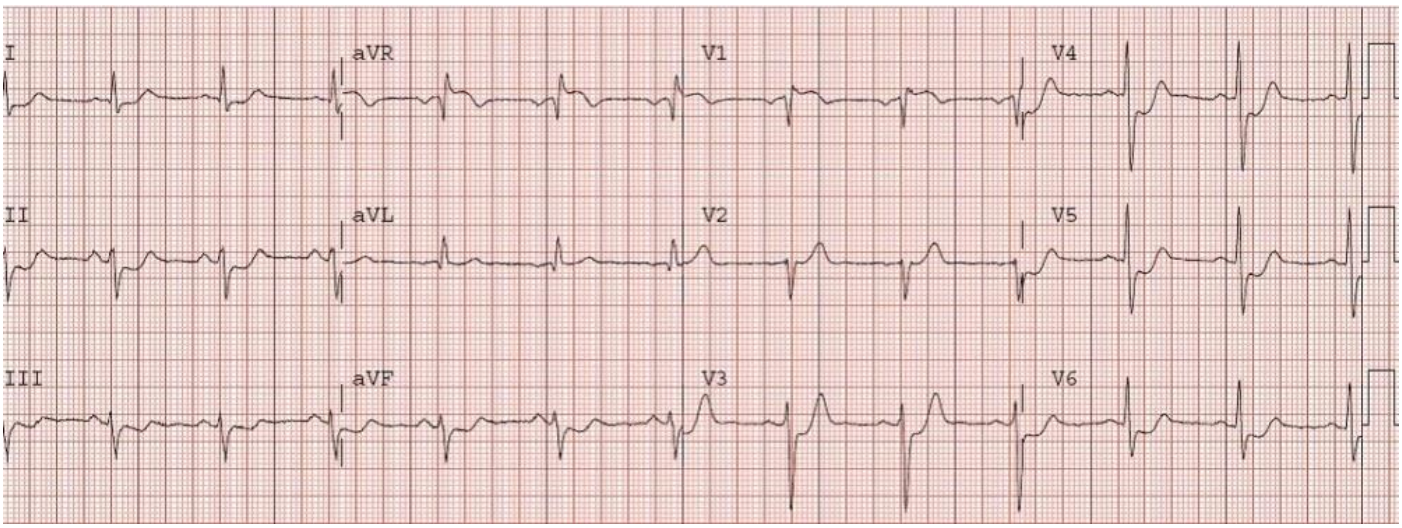
☑ Investigations:

The two most important investigations when assessing a patient with chest pain are:

- ✓ ECG
- ✓ Cardiac markers e.g. troponin



ECG showing a ST elevation myocardial infarction (STEMI). Note by how looking at which leads are affected (in this case II, III and aVF) we are able to tell which coronary arteries are blocked (the right coronary artery in this case). A blockage of the left anterior descending (LAD) artery would cause elevation of V1-V4, what is often termed an 'anterior' myocardial infarction.



ECG showing a non-ST elevation myocardial infarction (NSTEMI). On the ECG there is deep ST depression in I-III, aVF, and V3-V6. aVR also has ST elevation. Deep and widespread ST depression is associated with very high mortality because it signifies severe ischemia usually of LAD or left main stem.

The table below shows a simplified correlation between ECG changes and coronary territories:

	ECG changes	Coronary artery
Anterior	**V1-V4**	**Left anterior descending**
Inferior	**II, III, aVF**	**Right coronary**
Lateral	**I, V5-6**	**Left circumflex**

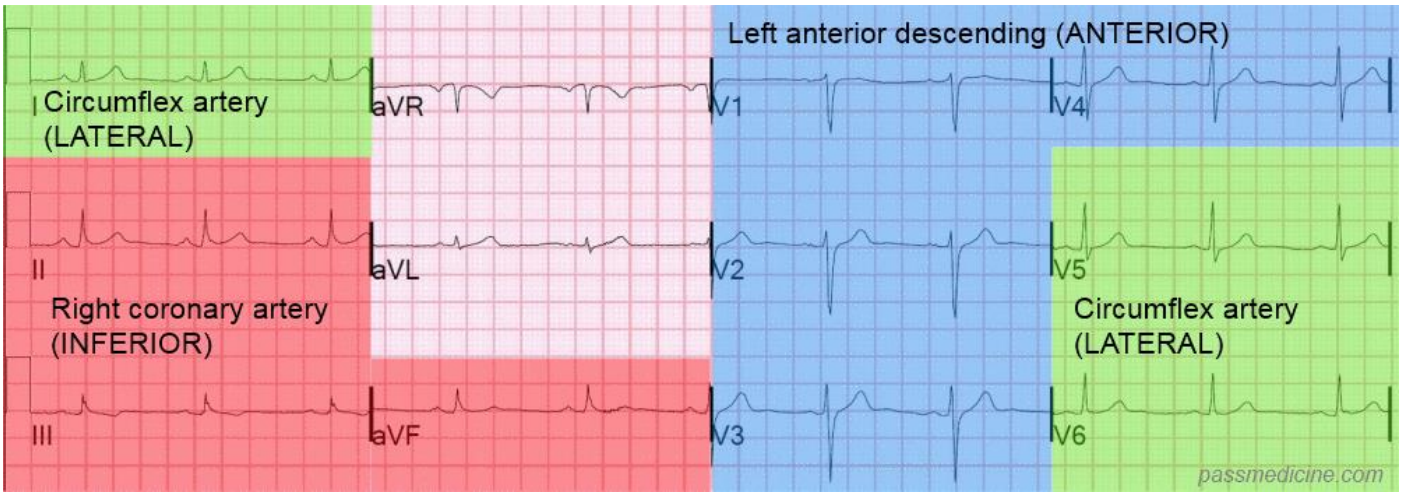


Diagram showing the correlation between ECG changes and coronary territories in acute coronary syndrome

☑ **Management:**

Once a diagnosis of ACS has been made there are a number of elements to treatment:

- ✓ Prevent worsening of presentation (i.e. further occlusion of coronary vessel)
- ✓ Revascularise (i.e. 'unblock') the vessel if occluded (patients presenting with a STEMI)
- ✓ Treat pain

☑ A commonly taught mnemonic for the treatment of ACS is MONA:

- ✓ Morphine
- ✓ Oxygen
- ✓ Nitrates
- ✓ Aspirin

☑ Whilst useful it should be remember that not all patients require oxygen therapy. British Thoracic Society guidelines are now widely adopted and oxygen should only be given if the oxygen saturations are < 94%.

☑ For patients who've had a **STEMI** (i.e. one of the coronary arteries has become occluded) the priority of management is to reopen, or revascularise, the blocked vessel.

- ✓ A second antiplatelet drug should be given in addition to aspirin. Options include clopidogrel, prasugrel and ticagrelor
- ✓ For many years the treatment of choice was thrombolysis. This involved the intravenous administration of a thrombolytic or 'clot-busting' drug to breakdown the thrombus blocking the coronary artery
- ✓ Since the early 2000's thrombolysis has been superseded by percutaneous coronary intervention (PCI). In this procedure the blocked arteries are opened up using a balloon (angioplasty) following which a stent may be deployed to prevent the artery occluding again in the future. This is done via a catheter inserted into either the radial or femoral artery

☑ If a patient presents with an **NSTEMI** then a risk stratification too (such as GRACE) is used to decide upon further management. If a patient is considered high-risk or is clinically unstable then coronary angiography will be performed during the admission. Lower risk patients may have a coronary angiogram at a later date.

☑ **Secondary prevention:**

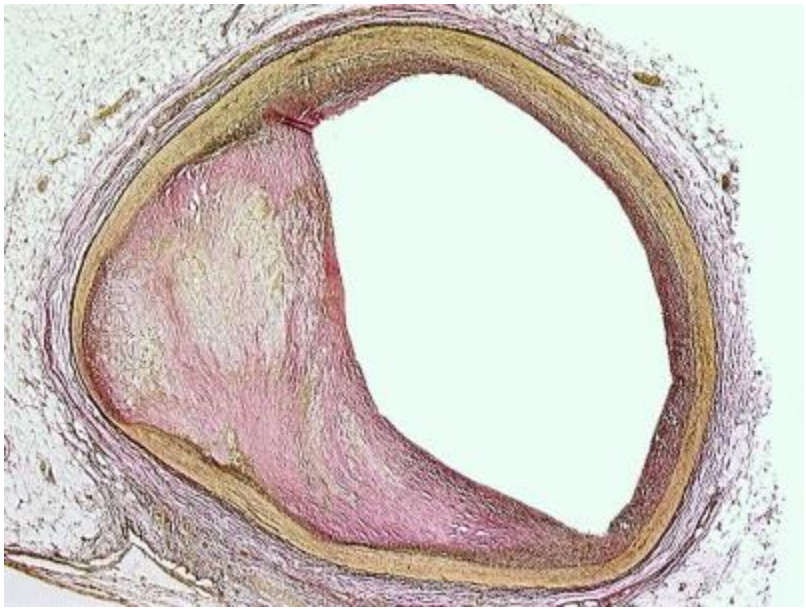
Patients who've had an ACS require lifelong drug therapy to help reduce the risk of a further event. Standard therapy comprises the following as a minimum:

- ✓ Aspirin
- ✓ A second antiplatelet if appropriate (e.g. clopidogrel)
- ✓ A beta-blocker
- ✓ **An ACE inhibitor**
- ✓ A statin

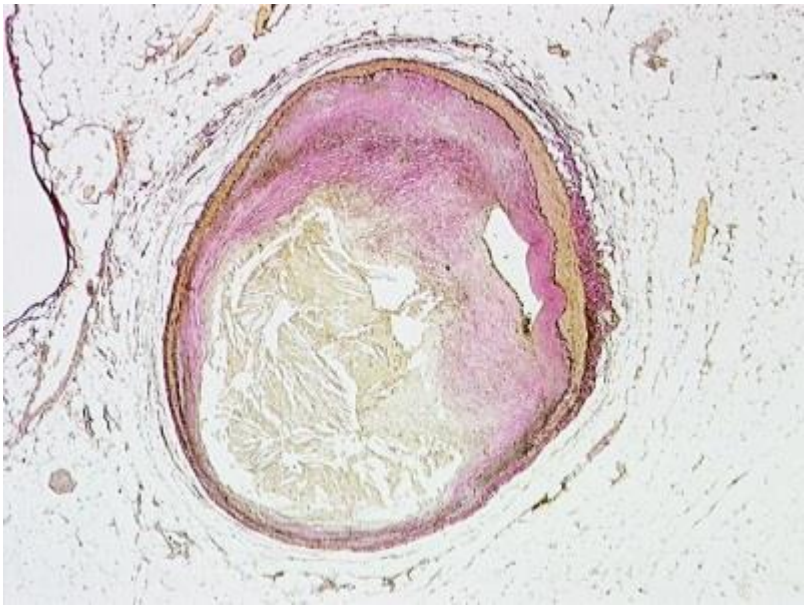
☑ **Further images:**

The following images show the progress of coronary artery atherosclerosis:

Normal coronary artery with blood in the lumen.



Moderately stenosed coronary artery, beetween 50-75%



Severely stenosed coronary artery

Recanalised old atherothrombotic occlusion of a coronary artery. Numerous small neolumina recanalising the organised occluding thrombus (indicated with arrows)

ACUTE CORONARY SYNDROME: INITIAL MANAGEMENT

Acute coronary syndrome (ACS) is a very common and important presentation in medicine. The management of ACS has evolved over recent years, with the development of new drugs and procedures such as percutaneous coronary intervention (PCI).

Emergency departments often have their own protocols based on local factors such as the availability of PCI and hospital drug formularies. The following is based on the 2020 update to the NICE ACS guidelines.

☑ **Acute coronary syndrome can be classified as follows:**

- ✓ **ST-elevation myocardial infarction (STEMI): ST-segment elevation + elevated biomarkers of myocardial damage**
- ✓ **Non ST-elevation myocardial infarction (NSTEMI): ECG changes but no ST-segment elevation + elevated biomarkers of myocardial damage**
- ✓ **Unstable angina**

☑ The management of ACS depends on the particular subtype. NICE management guidance groups the patients into two groups:

- ✓ 1. STEMI
- ✓ 2. NSTEM/unstable angina

☑ **Common management of all patients with ACS:**

☑ **Initial drug therapy**

- ✓ **Aspirin 300mg**
- ✓ Oxygen should only be given if the patient has oxygen saturations < 94% in keeping with British Thoracic Society oxygen therapy guidelines
- ✓ Morphine should only be given for patients with severe pain
  - Previously IV morphine was given routinely
  - Evidence, however, suggests that this may be associated with adverse outcomes
- ✓ Nitrates
  - Can be given either sublingually or intravenously
  - Useful if the patient has ongoing chest pain or hypertension
  - Should be used in caution if patient hypotensive

The next step in managing a patient with suspected ACS is to determine whether they meet the ECG criteria for STEMI. It is, of course, important to recognise that these criteria should be interpreted in the context of the clinical history.

☑ STEMI criteria

- ✓ Clinical symptoms consistent with ACS (generally of ≥ 20 minutes duration) with persistent (> 20 minutes) ECG features in ≥ 2 contiguous leads of:
  - 2.5 mm (i.e ≥ 2.5 small squares) ST elevation in leads V2-3 in men under 40 years, or ≥ 2.0 mm (i.e ≥ 2 small squares) ST elevation in leads V2-3 in men over 40 years
  - 1.5 mm ST elevation in V2-3 in women
  - 1 mm ST elevation in other leads
  - new LBBB (LBBB should be considered new unless there is evidence otherwise)

☑ Management of STEMI:

Once a STEMI has been confirmed the first step is to immediately assess eligibility for coronary reperfusion therapy. There are two types of coronary reperfusion therapy:

- ✓ **Percutaneous coronary intervention**
  - Should be offered if the presentation is within 12 hours of the onset of symptoms AND **PCI can be delivered within 120 minutes of the time** when fibrinolysis could have been given (i.e. consider fibrinolysis if there is a significant delay in being able to provide PCI)
  - If patients present after 12 hours and still have evidence of ongoing ischaemia then PCI should still be considered
  - Drug-eluting stents are now used. Previously 'bare-metal' stents were sometimes used but have higher rates of restenosis
  - Radial access is preferred to femoral access
- ✓ **Fibrinolysis**
  - **Should be offered within 12 hours of the onset of symptoms if primary PCI cannot be delivered within 120 minutes of the time when fibrinolysis could have been given**
  - A practical example may be a patient who presents with a STEMI to a small district general hospital (DGH) that does not have facilities for PCI. **If they cannot be transferred to a larger hospital for PCI within 120 minutes then fibrinolysis should be given. If the patient's ECG taken 90 minutes after fibrinolysis failed to show resolution of the ST elevation then they would then require transfer for PCI**

    If patients are eligible this should be offered as soon as possible.

☑ Percutaneous coronary intervention for patients with STEMI:

☑ Further antiplatelet prior to PCI

- ✓ This is termed 'dual antiplatelet therapy', i.e. aspirin + another drug
- ✓ **If the patient is not taking an oral anticoagulant: prasugrel**
- ✓ If taking an oral anticoagulant: clopidogrel

☑ Drug therapy during PCI

- ✓ Patients undergoing PCI with radial access:
  - **Unfractionated heparin with bailout glycoprotein IIb/IIIa inhibitor (GPI)** - this is the action of using a GPI during the procedure when it was not intended from the outset, e.g. because of worsening or persistent thrombus
- ✓ **Patients undergoing PCI with femoral access:**
  - **Bivalirudin with bailout GPI**

☑ Other procedures during PCI

- ✓ Thrombus aspiration, but not mechanical thrombus extraction, should be considered
- ✓ Complete revascularisation should be considered for patients with multivessel coronary artery disease without cardiogenic shock

☑ Fibrinolysis for patients with STEMI:

Fibrinolysis used to be the only form of coronary reperfusion therapy available. However, it is used much less commonly now given the widespread availability of PCI.

The contraindications to fibrinolysis and other factors are described in other notes.

Patients undergoing fibrinolysis should also be given an antithrombin drug.

An ECG should be repeated after 60-90 minutes to see if the ECG changes have resolved. If patients have persistent myocardial ischaemia following fibrinolysis then PCI should be considered.

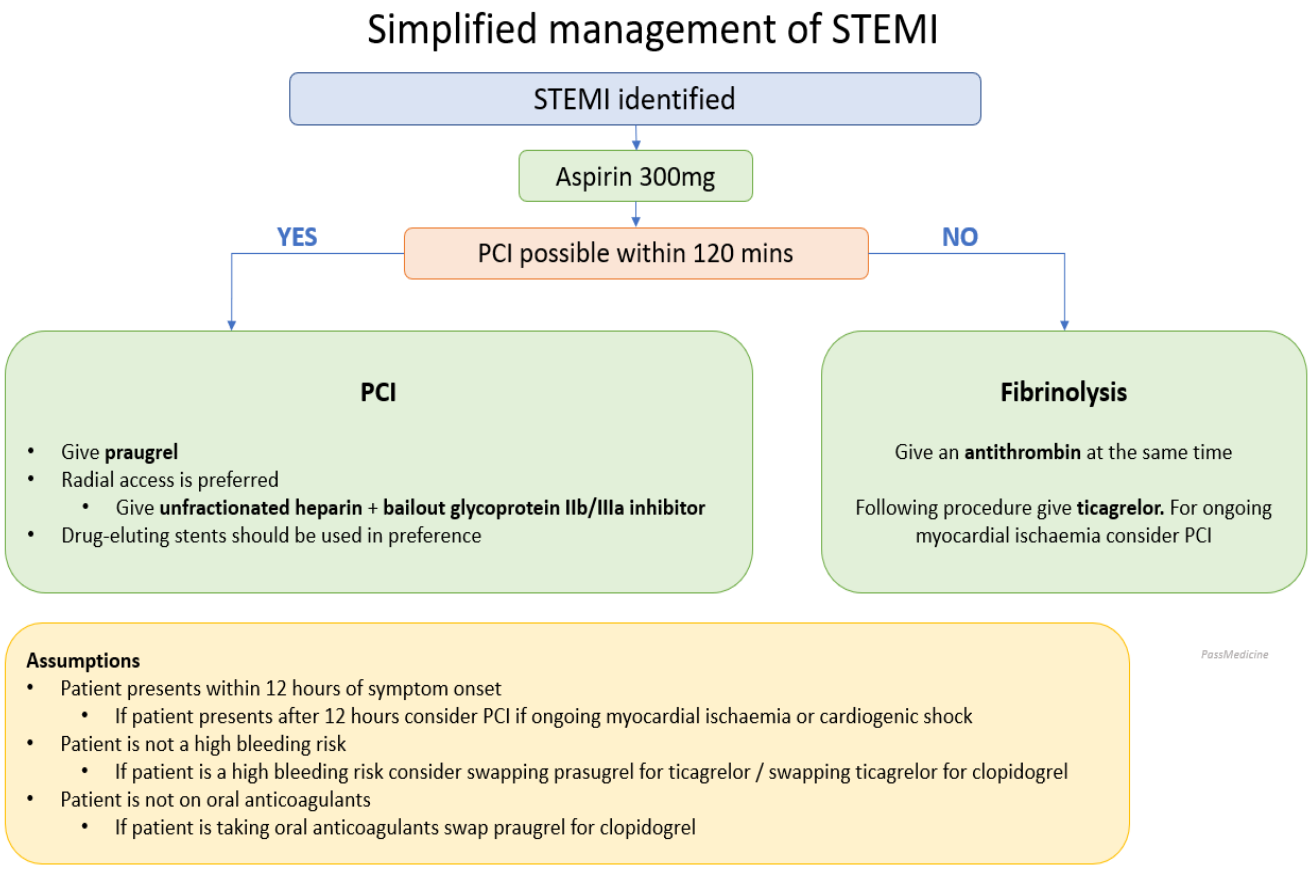


Diagram showing the simplified management of STEMI according to NICE guidelines. A number of assumptions (listed at the bottom) are made.

☑ Management of NSTEMI/unstable angina:

The management of NSTEMI/unstable angina is complicated and depends on individual patient factors and **a risk assessment**. The summary below provides an overview but the full NICE guidelines should be reviewed for further details.

☑ Further drug therapy

✓ Antithrombin treatment

- **Fondaparinux** should be offered to patients who are not at a high risk of bleeding and who are not having angiography immediately
- If immediate angiography is planned or a patients creatinine is > 265 µmol/L then unfractionated heparin should be given

☑ Risk assessment:

The Global Registry of Acute Coronary Events (GRACE) is the most widely used tool for risk assessment. It can be calculated using online tools and takes into account the **following factors:**

- ✓ Age
- ✓ Heart rate, blood pressure
- ✓ Cardiac (Killip class) and renal function (serum creatinine)
- ✓ Cardiac arrest on presentation
- ✓ ECG findings
- ✓ Troponin levels

This results in the patient being risk stratified as follows:

Predicted 6-month mortality	Risk of future adverse cardiovascular events
1.5% or below	Lowest
> 1.5% to 3.0%	Low
> 3.0% to 6.0%	Intermediate
> 6.0% to 9.0%	High
over 9.0%	Highest

Based on this risk assessment key decisions are made regarding whether a patient has coronary angiography (with follow-on PCI if necessary) or has conservative management. The detailed pros/cons of this decision are covered in other notes.

Which patients with NSTEMI/unstable angina should have coronary angiography (with follow-on PCI if necessary)?

- ✓ **Immediate: patient who are clinically unstable (e.g. hypotensive)**
- ✓ **Within 72 hours: patients with a GRACE score > 3% i.e. those at intermediate, high or highest risk**
- ✓ Coronary angiography should also be considered for patients if ischaemia is subsequently experienced after admission

☑ **Percutaneous coronary intervention for patients with NSTEMI/unstable angina:**

☑ **Further drug therapy**

- ✓ **Unfractionated heparin** should be given regardless of whether the patient has had fondaparinux or not
- ✓ Further antiplatelet ('dual antiplatelet therapy', i.e. aspirin + another drug) prior to PCI
  - If the patient is not taking an oral anticoagulant: prasugrel or ticagrelor
  - If taking an oral anticoagulant: clopidogrel

☑ **Conservative management for patients with NSTEMI/unstable angina:**

☑ **Further drug therapy**

- ✓ **Further antiplatelet** ('dual antiplatelet therapy', i.e. aspirin + another drug)
  - If the patient is not at a high risk of bleeding: ticagrelor
  - If the patient is at a high risk of bleeding: clopidogrel

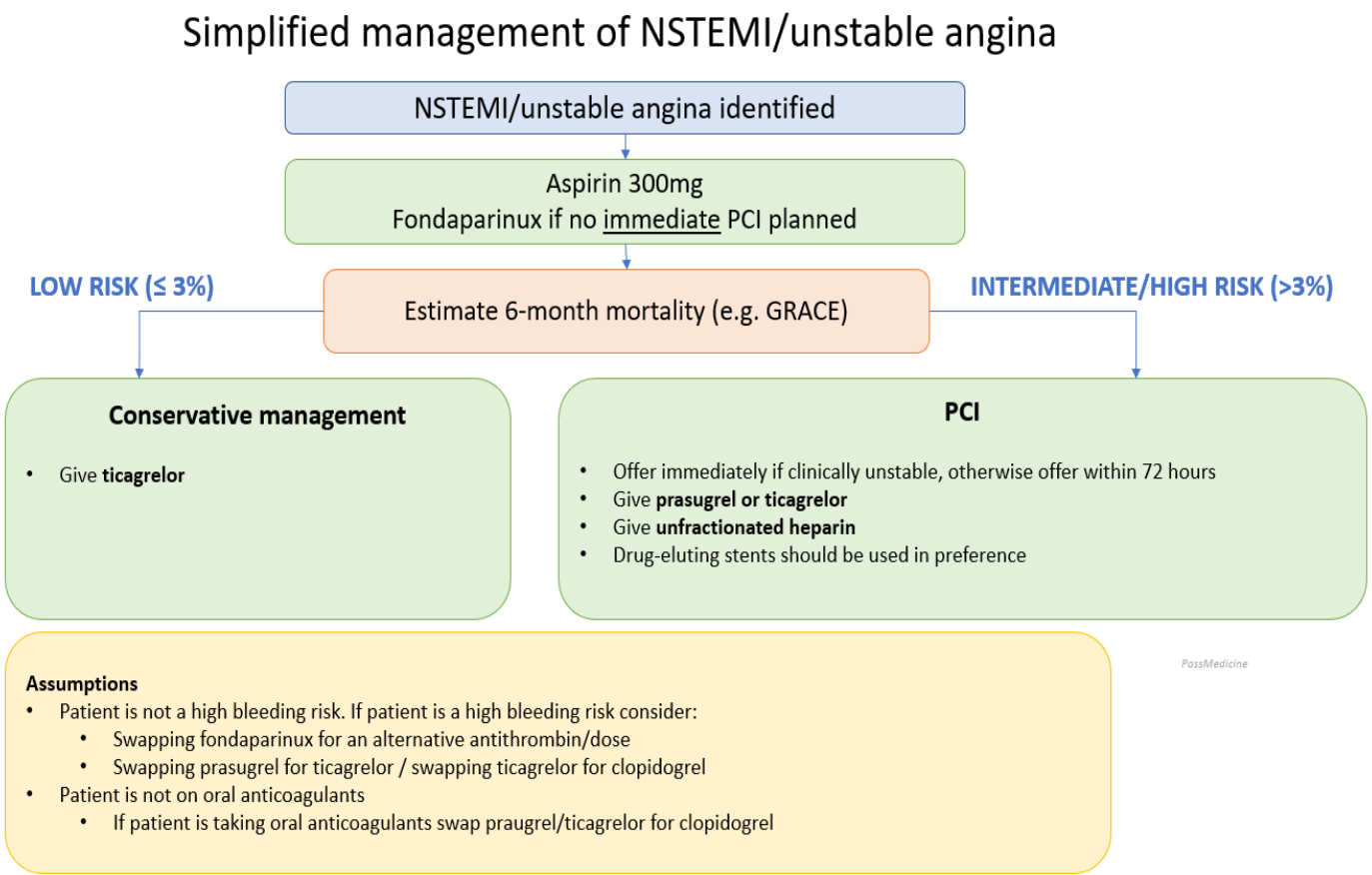


Diagram showing the simplified management of NSTEMI/unstable angina according to NICE guidelines. A number of assumptions (listed at the bottom) are made.

BIVALIRUDIN

Bivalirudin is a reversible Direct Thrombin Inhibitor used as an anticoagulant in the management of acute coronary syndrome.

MYOCARDIAL INFARCTION: STEMI MANAGEMENT

A number of studies over the past 10 years have provided an evidence for the management of ST-elevation myocardial infarction (STEMI)

☑ In the absence of contraindications, **all patients should be given**
- ✓ **Aspirin**
- ✓ **P2Y12-receptor antagonist**. Clopidogrel was the first P2Y12-receptor antagonist to be widely used but now ticagrelor is often favoured as studies have shown improved outcomes compared to clopidogrel, but at the expense of slightly higher rates of bleeding. This approached is supported in SIGN's 2016 guidelines. They also recommend that prasugrel (another P2Y12-receptor antagonist) could be considered if the patient is going to have a percutaneous coronary intervention
- ✓ **Unfractionated heparin** is usually given for patients who're are going to have a PCI. Alternatives include low-molecular weight heparin

☑ **NICE suggest the following in terms of oxygen therapy:**
- ✓ Do not routinely administer oxygen, but monitor oxygen saturation using pulse oximetry as soon as possible, ideally before hospital admission. Only offer supplemental oxygen to:
- ✓ People with oxygen saturation (SpO2) of less than 94% who are not at risk of hypercapnic respiratory failure, aiming for SpO2 of 94-98%
- ✓ People with chronic obstructive pulmonary disease who are at risk of hypercapnic respiratory failure, to achieve a target SpO2 of 88-92% until blood gas analysis is available.

☑ **Primary percutaneous coronary intervention (PCI) has emerged as the gold-standard treatment for STEMI** but is not available in all centres. Thrombolysis should be performed in patients without access to primary PCI

☑ **With regards to thrombolysis:**
- ✓ Tissue plasminogen activator (tPA) has been shown to offer clear mortality benefits over streptokinase
- ✓ **Tenecteplase** is easier to administer and has been shown to have non-inferior efficacy to alteplase with a similar adverse effect profile

☑ An ECG should be performed 90 minutes following thrombolysis to assess whether there has been a greater than 50% resolution in the ST elevation
- ✓ If there has not been adequate resolution then rescue PCI is superior to repeat thrombolysis
- ✓ For patients successfully treated with thrombolysis PCI has been shown to be beneficial. The optimal timing of this is still under investigation

☑ **Glycaemic control in patients with diabetes mellitus**
- ✓ In 2011 NICE issued guidance on the management of hyperglycaemia in acute coronary syndromes
- ✓ It recommends using a dose-adjusted insulin infusion with regular monitoring of blood glucose levels to glucose below 11.0 mmol/l
- ✓ Intensive insulin therapy (an intravenous infusion of insulin and glucose with or without potassium, sometimes referred to as 'DIGAMI') regimes are not recommended routinely

ACUTE CORONARY SYNDROME: PROGNOSTIC FACTORS

The 2006 Global Registry of Acute Coronary Events (GRACE) study has been used to derive regression models to predict death in hospital and death after discharge in patients with acute coronary syndrome

☑ **Poor prognostic factors**
- ✓ Age
- ✓ Development (or history) of heart failure
- ✓ Peripheral vascular disease
- ✓ Reduced systolic blood pressure
- ✓ Killip class*
- ✓ Initial serum creatinine concentration
- ✓ Elevated initial cardiac markers
- ✓ Cardiac arrest on admission
- ✓ ST segment deviation

☑ ***Killip class** - system used to stratify risk post myocardial infarction

Killip class	Features	30 day mortality
I	No clinical signs heart failure	6%
II	Lung crackles, S3	17%
III	Frank pulmonary oedema	38%
IV	Cardiogenic shock	81%

ANGINA PECTORIS: DRUG MANAGEMENT

The management of stable angina comprises lifestyle changes, medication, percutaneous coronary intervention and surgery. NICE produced guidelines in 2011 covering the management of stable angina

☑ Medication

- ✓ All patients should receive aspirin and a statin in the absence of any contraindication
- ✓ Sublingual glyceryl trinitrate to abort angina attacks
- ✓ NICE recommend using either **a Beta-Blocker or a Calcium channel blocker first-line** based on 'comorbidities, contraindications and the person's preference'
- ✓ If a calcium channel blocker is used as monotherapy a rate-limiting one such as verapamil or diltiazem should be used. **If used in combination with a Beta-Blocker then use a long-acting Dihydropyridine Calcium-channel blocker (e.g. modified-release Nifedipine).** Remember that beta-blockers should not be prescribed concurrently with verapamil (risk of complete heart block)
- ✓ If there is a poor response to initial treatment then medication should be **increased to the maximum tolerated dose (e.g. for Atenolol 100mg od)**
- ✓ If a patient is still symptomatic after monotherapy with **a Beta-Blocker add a Calcium channel blocker and vice versa**
- ✓ If a patient is on monotherapy and cannot tolerate the addition of a calcium channel blocker or a beta-blocker then consider one of the following drugs: **a long-acting Nitrate, Ivabradine, Nicorandil or Ranolazine**
- ✓ If a patient is taking both a beta-blocker and a calcium-channel blocker then **only add a third drug whilst a patient is awaiting assessment for PCI or CABG**

☑ Nitrate tolerance

- ✓ Many patients who take nitrates develop tolerance and experience reduced efficacy
- ✓ NICE advises that patients who take standard-release isosorbide mononitrate should use an **asymmetric dosing interval to maintain a daily nitrate-free time** of 10-14 hours to minimise the development of nitrate tolerance
- ✓ This effect is not seen in patients who take once-daily modified-release isosorbide mononitrate

NITRATES

Nitrates are a group of drugs which have vasodilating effects. The main indications for their use is in the management of angina and the acute treatment of heart failure. Sublingual glyceryl trinitrate is the most common drug used in patients with ischaemic heart disease to relieve angina attacks.

☑ **Mechanism of action**

- ✓ **Nitrates cause the release of nitric oxide in smooth muscle, activating guanylate cyclase which then converts GTP to cGMP,** which in turn leads to a fall in intracellular calcium levels
- ✓ In angina they both dilate the coronary arteries and also reduce venous return which in turn reduces left ventricular work, reducing myocardial oxygen demand

☑ **Side-effects**

- ✓ **Hypotension**
- ✓ **Tachycardia**
- ✓ **Headaches**
- ✓ **Flushing**

☑ **Nitrate tolerance**

- ✓ Many patients who take nitrates develop tolerance and experience reduced efficacy
- ✓ The BNF advises that patients who develop tolerance should take the second dose of **isosorbide mononitrate after 8 hours, rather than after 12 hours**. This allows blood-nitrate levels to fall for 4 hours and maintains effectiveness
- ✓ This effect is not seen in patients who take modified release isosorbide mononitrate

NICORANDIL

Nicorandil is a vasodilatory drug used to treat angina. It is a **potassium-channel activator with vasodilation is through activation of guanylyl cyclase which results in increase cGMP.**

☑ **Adverse effects**

- ✓ **Headache**
- ✓ **Flushing**
- ✓ Skin, mucosal and eye ulceration
  - **Gastrointestinal ulcers** including **anal ulceration**

☑ **Contraindications**

- ✓ **Left ventricular failure**

SIDE-EFFECTS OF COMMON DRUGS: ANTI-ANGINALS

The table below summarises characteristic (if not necessarily the most common) side-effects of drugs used to treat angina

Drug	Side-effect
Calcium channel blockers	✓ Headache ✓ **Flushing** ✓ **Ankle oedema** Verapamil also commonly causes constipation
Beta-blockers	✓ **Bronchospasm (especially in asthmatics)** ✓ Fatigue ✓ **Cold peripheries** ✓ Sleep disturbances
Nitrates	✓ **Headache** ✓ **Postural hypotension** ✓ **Tachycardia**
Nicorandil	✓ **Headache** ✓ **Flushing** ✓ **Anal ulceration**

PERCUTANEOUS CORONARY INTERVENTION

Percutaneous coronary intervention (PCI) is a technique used to restore myocardial perfusion in patients with ischaemic heart disease, both in patients with stable angina and acute coronary syndromes. Stents are implanted in around 95% of patients - it is now rare for just balloon angioplasty to be performed

Following stent insertion migration and proliferation of smooth muscle cells and fibroblasts occur to the treated segment. The stent struts eventually become covered by endothelium. Until this happens there is an increased risk of platelet aggregation leading to thrombosis.

☑ **Two main complications may occur**

✓ **Stent thrombosis**: due to platelet aggregation as above. Occurs in 1-2% of patients, most **commonly in the first month**. Usually presents with acute myocardial infarction

- ✓ **Restenosis:** due to excessive tissue proliferation around stent. Occurs in around 5-20% of patients, **most commonly in the first 3-6 months**. Usually presents with the recurrence of angina symptoms. **Risk factors include diabetes, renal impairment and stents in venous bypass grafts**

☑ **Types of stent**

- ✓ Bare-metal stent (BMS)
- ✓ Drug-eluting stents (DES): stent coated with paclitaxel or rapamycin which inhibit local tissue growth. Whilst this reduces restenosis rates the stent thrombosis rates are increased as the process of stent endothelisation is slowed

☑ Following insertion, **the most important factor in preventing stent thrombosis is antiplatelet therapy. Aspirin should be continued indefinitely**. The length of clopidogrel treatment depends on the type of stent, reason for insertion and consultant preference. Antiplatelets should only be stopped following discussion with the cardiology team (e.g. if the patient is due to have surgery) due to the risk of stent thrombosis.

THROMBOLYSIS

Thrombolytic drugs activate plasminogen to form plasmin. This in turn degrades fibrin and help breaks up thrombi. They in primarily used in patients who present with a ST elevation myocardial infarction. Other indications include acute ischaemic stroke and pulmonary embolism, although strict inclusion criteria apply.

☑ **Examples**

- ✓ Alteplase
- ✓ Tenecteplase
- ✓ Streptokinase

☑ **Contraindications to thrombolysis**

- ✓ Active internal bleeding
- ✓ Recent haemorrhage, trauma or surgery (including dental extraction)
- ✓ Coagulation and bleeding disorders
- ✓ Intracranial neoplasm
- ✓ Stroke < 3 months
- ✓ Aortic dissection
- ✓ Recent head injury
- ✓ Severe hypertension

☑ **Side-effects**

- ✓ Haemorrhage
- ✓ Hypotension - more common with streptokinase
- ✓ Allergic reactions may occur with streptokinase

MYOCARDIAL INFARCTION: COMPLICATIONS

Patients are at risk of a number of immediate, early and late complications following a myocardial infarction (MI).

☑ **Cardiac arrest:**

This most commonly occurs due to patients developing **ventricular fibrillation and is the most common cause of death following a MI**. Patients are managed as per the ALS protocol with defibrillation.

☑ **Cardiogenic shock:**

If a large part of the ventricular myocardium is damaged in the infarction the ejection fraction of the heart may decrease to the point that the patient develops cardiogenic shock. This is difficult to treat. Other causes of cardiogenic shock include the 'mechanical' complications such as left ventricular free wall rupture as listed below. Patients may require inotropic support and/or an intra-aortic balloon pump.

☑ **Chronic heart failure:**

As described above, if the patient survives the acute phase their ventricular myocardium may be dysfunctional resulting in chronic heart failure. Loop diuretics such as furosemide will decrease fluid overload. **Both ACE-inhibitors and beta-blockers have been shown to improve the long-term prognosis of patients with chronic heart failure.**

☑ **Tachyarrhythmias:**

Ventricular fibrillation, as mentioned above, is the most common cause of death following a MI. Other common arrhythmias including ventricular tachycardia.

☑ **Bradyarrhythmias:**

Atrioventricular block is more common following inferior myocardial infarctions.

☑ **Pericarditis:**

Pericarditis in the first 48 hours following a transmural MI is common (c. 10% of patients). The pain is typical for pericarditis (worse on lying flat etc), a pericardial rub may be heard and a pericardial effusion may be demonstrated with an echocardiogram.

Dressler's syndrome tends to occur around 2-6 weeks following a MI. The underlying pathophysiology is thought to be an autoimmune reaction against antigenic proteins formed as the myocardium recovers. **It is characterised by a combination of fever, pleuritic pain, pericardial effusion and a raised ESR. It is treated with NSAIDs.**

☑ **Left ventricular aneurysm:**

The ischaemic damage sustained may weaken the myocardium resulting in aneurysm formation. This is typically associated **with persistent ST elevation and left ventricular failure**. Thrombus may form within the aneurysm increasing the risk of stroke. Patients are therefore anticoagulated.

☑ **Left ventricular free wall rupture:**

This is seen in around 3% of MIs and occurs around 1-2 weeks afterwards. Patients present with acute heart failure secondary to cardiac tamponade (**raised JVP, pulsus paradoxus, diminished heart sounds). Urgent pericardiocentesis and thoracotomy are required.**

☑ **Ventricular septal defect:**

Rupture of the interventricular septum usually occurs in the first week and is seen in around 1-2% of patients. Features: acute heart failure associated with a **pan-systolic murmur. An echocardiogram is diagnostic** and will exclude acute mitral regurgitation which presents in a similar fashion. Urgent surgical correction is needed.

☑ **Acute mitral regurgitation:**

More common with infero-posterior infarction and may be due to **ischaemia or rupture of the papillary muscle.** Acute hypotension and pulmonary oedema may occur. An early-to-mid systolic murmur is typically heard. Patients are treated with vasodilator therapy but often require emergency surgical repair.

MYOCARDIAL INFARCTION: SECONDARY PREVENTION

NICE produced guidelines on the management of patients following a myocardial infarction (MI) in 2013. Some key points are listed below

All patients should be offered the following drugs:

- ✓ Dual antiplatelet therapy (aspirin plus a second antiplatelet agent)
- ✓ ACE inhibitor
- ✓ beta-blocker
- ✓ Statin

☑ **Some selected lifestyle points:**

- ✓ Diet: advise a Mediterranean style diet, switch butter and cheese for plant oil based products. Do not recommend omega-3 supplements or eating oily fish
- ✓ Exercise: advise 20-30 mins a day until patients are 'slightly breathless'
- ✓ Sexual activity may resume 4 weeks after an uncomplicated MI. Reassure patients that sex does not increase their likelihood of a further MI. PDE5 inhibitors (e.g, sildenafil) may be used 6 months after a MI. They should however be avoided in patient prescribed either nitrates or nicorandil

☑ Most patients who've had an acute coronary syndrome are now given dual antiplatelet therapy (DAPT). Clopidogrel was previously the second antiplatelet of choice. Now ticagrelor and prasugrel (also ADP-receptor inhibitors) are more widely used. The NICE Clinical Knowledge Summaries now recommend:

- ✓ Post acute coronary syndrome (medically managed): add ticagrelor to aspirin, stop ticagrelor after 12 months
- ✓ Post percutaneous coronary intervention: add prasugrel or ticagrelor to aspirin, stop the second antiplatelet after 12 months
- ✓ This 12 month period may be altered for people at a high-risk of bleeding or those who at high-risk of further ischaemic events

☑ **Aldosterone antagonists**

- ✓ Patients who have had an **acute MI and who have symptoms and/or signs of heart failure and left ventricular systolic dysfunction, treatment with an aldosterone antagonist** licensed for post-MI treatment (e.g. eplerenone) should be initiated within 3-14 days of the MI, preferably after ACE inhibitor therapy

COMBINATION ANTIPLATELET AND ANTICOAGULANT THERAPY

With the increase in comorbidity, it is now common to find that a patient has an indication for both an antiplatelet (e.g. established cardiovascular disease) and an anticoagulant (e.g. atrial fibrillation, venous thromboembolism or valvular heart disease). However, combination therapy increases the risk of bleeding and may not be needed in all cases. How should this be managed?

Whilst there are not guidelines to cover every scenario a recent review in the BMJ offered an expert opinion outlining the approach in common scenarios.

☑ Secondary prevention of stable cardiovascular disease with an indication for an anticoagulant

- ✓ Normally in this situation, all patients are recommended to be prescribed an antiplatelet
- ✓ If an indication for anticoagulant exists (for example atrial fibrillation) it is indicated that **anticoagulant monotherapy is given without the addition of antiplatelets**

☑ Post-acute coronary syndrome/percutaneous coronary intervention

- ✓ In these patients, there is a much stronger indication for antiplatelet therapy
- ✓ Generally **patients are given triple therapy (2 antiplatelets + 1 anticoagulant) for 4 weeks-6 months after the event and dual therapy (1 antiplatelet + 1 anticoagulant) to complete 12 months**
- ✓ There is variation from patient to patient however given that the stroke risk in atrial fibrillation varies according to risk factors.

☑ Venous thromboembolism (VTE)

- ✓ If a patient on antiplatelets develops a VTE they are likely to be prescribed anticoagulants for 3-6 months
- ✓ A HAS-BLED score should be calculated. **Those with a low risk of bleeding may continue antiplatelets. In patients with an intermediate or high risk of bleeding consideration should be given to stopping the antiplatelets**

ANTIPLATELETS: SUMMARY OF LATEST GUIDANCE

The table below summarises the most recent guidelines regarding antiplatelets:

Diagnosis	1st line	2nd line
Acute coronary syndrome (medically treated)	**Aspirin (lifelong) & ticagrelor (12 months)**	If aspirin contraindicated, clopidogrel (lifelong)
Percutaneous coronary intervention	**Aspirin (lifelong) & prasurgrel or ticagrelor (12 months)**	**If aspirin contraindicated, clopidogrel (lifelong)**
TIA	**Clopidogrel (lifelong)**	**Aspirin (lifelong) & dipyridamole (lifelong)**
Ischaemic stroke	**Clopidogrel (lifelong)**	**Aspirin (lifelong) & dipyridamole (lifelong)**
Peripheral arterial disease	**Clopidogrel (lifelong)**	**Asprin (lifelong)**

ASPIRIN

Aspirin works by blocking the action of both cyclooxygenase-1 and 2. Cyclooxygenase is responsible for prostaglandin, prostacyclin and thromboxane synthesis. **The blocking of thromboxane A2 formation** in platelets reduces the ability of platelets to aggregate which has lead to the widespread use of low-dose aspirin in cardiovascular disease. Until recent guidelines changed all patients with established cardiovascular disease took aspirin if there was no contraindication. Following the 2010 technology appraisal of clopidogrel this is no longer the case*.

Two recent trials (the Aspirin for Asymptomatic Atherosclerosis and the Antithrombotic Trialists Collaboration) have cast doubt on the use of aspirin in primary prevention of cardiovascular disease. Guidelines have not yet changed to reflect this. However the Medicines and Healthcare products Regulatory Agency (MHRA) issued a drug safety update in January 2010 reminding prescribers that aspirin is not licensed for primary prevention.

☑ **What do the *current* guidelines recommend?**

- ✓ First-line for patients with ischaemic heart disease

☑ **Potentiates**

- ✓ Oral hypoglycaemics
- ✓ Warfarin
- ✓ Steroids

☑ **Aspirin should not be used in children under 16 due to the risk of Reye's syndrome. An exception is Kawasaki disease,** where the benefits are thought to outweigh the risks.

*NICE now recommend clopidogrel first-line following an ischaemic stroke and for peripheral arterial disease. For TIAs the situation is more complex. Recent Royal College of Physician (RCP) guidelines support the use of clopidogrel in TIAs. However the older NICE guidelines still recommend aspirin + dipyridamole - a position the RCP state is 'illogical'

ADENOSINE DIPHOSPHATE (ADP) RECEPTOR INHIBITORS

☑ **Examples include:**

- ✓ Clopidogrel
- ✓ Prasugrel
- ✓ Ticagrelor
- ✓ Ticlopidine

☑ **Mechanism of ADP receptor inhibitors**

- ✓ Adenosine diphosphate (ADP) is one of the main platelet activation factors, mediated by G-coupled receptors P2Y1 and P2Y12.
- ✓ The main target of ADP receptor inhibition is the P2Y12 receptor, as it is the one which leads to sustained platelet aggregation and stabilisation of the platelet plaque.

☑ **Evidence**

- ✓ As aspirin and ADP inhibitors work by blocking different platelet aggregation pathways, their potential synergy has been studied by multiple clinical trials, particularly in high-risk patients presenting with acute coronary syndrome (ACS) or undergoing percutaneous coronary intervention (PCI).
- ✓ Clopidogrel used to be the most commonly used ADP inhibitor, however, due to its interindividual variability in antiplatelet effects, newer agents such as prasugrel and ticagrelor have been developed.
- ✓ Multiple trials since have shown a marked reduction in short- and long-term ischaemic events when using prasugrel and aspirin, compared to clopidogrel and aspirin in moderate- to high-risk ACS patients.[1]
- ✓ Current NICE guidelines for ACS, therefore, recommend starting dual antiplatelet treatment (DAPT) with Aspirin (75mg daily) and Ticagrelor (90mg twice daily) for 12 months, as a secondary prevention strategy.

- ✓ NICE guidelines for people with ACS undergoing PCI recommend aspirin (75-100mg daily) in combination with either prasugrel (10mg daily), ticagrelor (90mg twice daily), or clopidogrel (75mg daily, if prasugrel or ticagrelor are not suitable) for 12 months, with aspirin alone thereafter.

☑ **Notable adverse effects**

- ✓ **Ticagrelor may cause dyspnoea**
  - **Due to the impaired clearance of adenosine**

☑ **Interactions and contraindications**

- ✓ A drug interaction exists between clopidogrel and proton pump inhibitors, particularly **omeprazole and esomeprazole, leading to reducing antiplatelet effects.**
- ✓ **Patients with prior stroke or transient ischaemic attack, high risk of bleeding, and prasugrel hypersensitivity are absolute contraindications to prasugrel use.**
- ✓ Ticagrelor is contraindicated in patients with a high risk of bleeding, those with a history of intracranial haemorrhage, and those with severe hepatic dysfunction. It is also to be used with caution in those with **acute asthma or COPD**, as ticagrelor-treated patients experience higher rates of dyspnoea.

CLOPIDOGREL

Clopidogrel is an antiplatelet agent used in the management of cardiovascular disease. It was previously used when aspirin was not tolerated or contraindicated but there are now a number of conditions for which clopidogrel is used in addition to aspirin, for example in patients with an acute coronary syndrome. Following the 2010 NICE technology appraisal clopidogrel is also now first-line in patients following an ischaemic stroke and in patients with peripheral arterial disease.

Clopidogrel belongs to a class of drugs known as thienopyridines which have a similar mechanism of action. Other examples include:

- ✓ Prasugrel
- ✓ Ticagrelor
- ✓ Ticlopidine

☑ **Mechanism**

- ✓ **Antagonist of the $P2Y_{12}$ adenosine diphosphate (ADP) receptor,** inhibiting the activation of platelets

☑ **Interactions**

- ✓ **Concurrent use of proton pump inhibitors (PPIs) may make clopidogrel less effective** (MHRA July 2009)
- ✓ This advice was updated by the MHRA in April 2010, evidence seems inconsistent but omeprazole and esomeprazole still cause for concern. Other PPIs such as **lansoprazole should be OK -** please see the link for more details

DIPYRIDAMOLE

Dipyridamole is an antiplatelet mainly used in combination with aspirin after an ischaemic stroke or transient ischaemic attack.

☑ **Mechanism of action**

- ✓ **Inhibits phosphodiesterase, elevating platelet cAMP levels which in turn reduce intracellular calcium levels**
- ✓ **Other actions include reducing cellular uptake of adenosine and inhibition of thromboxane synthase**